



Biotechnology Innovation Organization
1201 New York Ave., NW
Suite 1300
Washington, DC, 20005
202-962-9200

November 17, 2023

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. 2016-D-0643: Labeling for Biosimilar and Interchangeable Biosimilar Products

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the request for information and comments on the Agency's Draft Guidance: **Labeling for Biosimilar and Interchangeable Biosimilar Products (Draft Guidance)**.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place. BIO represents both innovator and biosimilar manufacturers and respectfully requests that as the Agency seeks to refine and/or develop new policies related to biosimilar and interchangeable biosimilar products that it solicits feedback from all stakeholders.

Specific Comments

1. Interchangeability Statement on Product Labeling

Implementation of the Biologics Price Competition and Innovation Act (BPCIA), including the distinction between biosimilar and interchangeable products remains of significant importance to BIO members and BIO wants to avoid any erosion of the distinction between biosimilar and interchangeable, even in labeling. As you know, an interchangeable biological product is a biosimilar that meets additional statutory requirements that enable substitution for the reference product at the pharmacy. By removing the clear identification of interchangeability from the product label, BIO believes that FDA undermines the statute by standardizing the label to "biosimilar" thereby encouraging the perception that all biosimilars can be considered as interchangeable at the pharmacy. BIO is also concerned this change may lead to unintended consequences. For example, promotional labeling or advertising could imply that a biosimilar is interchangeable when it is not, mischaracterizing both the statutory distinction between a biosimilar and an interchangeable product and imply that the biosimilar has satisfied the requirements for interchangeability set forth in section 351(k)(4) when it has not. Therefore, BIO recommends that FDA retain the interchangeability statement in the label for those products which have been determined to be interchangeable.



BIO appreciates FDA's acknowledgement in the Federal Register Notice for this draft guidance that interchangeability plays a role with respect to pharmacy substitution and pharmacists, and we support inclusion of footnote 7 in line 66 of the Draft Guidance. However, FDA's assertion that "a labeling statement noting that certain products within a 351(k) BLA have been approved as interchangeable, and explaining the interchangeability standard, is not likely to be useful to prescribers" is not supported. Physicians and patients have a right to understand additional clinical evidence concerning drugs being prescribed and taken by patients. Misconceptions and confusion around interchangeability will not be addressed by eliminating information pertaining to the topic from product labels. Currently, there is no evidence that demonstrates interchangeability is the cause of: (1) any confusion to physicians and patients and (2) that the interchangeability designation is a barrier to biosimilar market uptake. BIO believes it is important for FDA, as an authoritative source, to convey that interchangeability relates to pharmacy substitution, which helps stakeholders understand that biosimilar products are as safe and effective as their respective reference biological products and are not inferior to interchangeable biosimilar products. The label is the main source of product information for patients, healthcare professionals (HCPs), including pharmacists, and the public in general. The Purple Book (available only via the FDA website) is not a routinely accessed source document used by patients and HCPs and is not commonly recognized in the same way as the product label. In particular, physicians rely heavily on the label when prescribing medications and when looking for information about the product and have indicated their preference to refer to one source to obtain relevant information.^{1,2} Retaining the interchangeability statement in labeling and explaining the standard is an important step towards education around the meaning of the interchangeability standard.

If the Agency does not change its position on the interchangeability statement, BIO notes there are interchangeable biosimilar products currently on the market whose labels contain interchangeability statements. Implementation of the guidance to subsequently approved interchangeable biosimilars resulting in two interchangeable biosimilars to the same reference product having different labels, one described as an interchangeable biosimilar (with the associated explanation of interchangeable) and the other described as biosimilar (with the associated explanation of biosimilar), may lead to confusion. If the Agency cannot retrospectively apply these recommendations to the labels of interchangeable products already on the market, then we recommend that the label of any interchangeable biosimilar subsequently approved for the same reference product as the previously approved interchangeable biosimilar should specifically denote that it is interchangeable to ensure that

¹ Sullivan HW, Squire C, Aikin KJ, Tzeng J, Ferriola-Bruckenstein K, Brodsky E, Trentacosti AM, Johnson M. Physicians' use of and preferences for FDA-approved prescribing information. *Res Social Adm Pharm*. 2022 Jun;18(6):3027-3037. doi: 10.1016/j.sapharm.2021.07.028. Epub 2021 Aug 1. PMID: 34364803; PMCID: PMC8803992.

² Hallersten A, Fürst W, Mezzasalma R. Physicians prefer greater detail in the biosimilar label (SmPC) - Results of a survey across seven European countries. *Regul Toxicol Pharmacol*. 2016 Jun;77:275-81. doi: 10.1016/j.yrtph.2016.03.021. Epub 2016 Apr 1. PMID: 27041395.



inconsistent labeling is not cause for actual confusion. However, BIO strongly suggests that the Agency should not change its position on the interchangeability statement.

2. Biosimilar Statement on Product Labeling

BIO supports maintaining the biosimilar statement in the product labeling, as proposed in the Draft Guidance. We believe this statement is important given the use of product-specific naming associated with particular data in biosimilar product labeling; for example, the biosimilar statement may help provide clarity to HCPs when reading and interpreting the data and information in the labeling (some of which concerns the biosimilar and some of which concerns the reference product). BIO also notes that this is consistent with the approach taken in the European Union, where biosimilar labeling includes a statement noting that the product is biosimilar.

3. Naming convention

In several sections of the Draft Guidance there is mention of the reference product proper name with the four-letter suffix. However, in some cases, the reference product will not have a suffix. In these circumstances and where the Draft Guidance indicates to include the proper name of the reference product (ie. replicamab-hjxf) in the biosimilar/interchangeable biosimilar product labeling (such as in Table 1 and lines 293-297), BIO recommends that the final guidance clearly state that the proper name be used regardless of whether the reference product has a four-letter suffix.

Respectfully Submitted,

/s/

Neil Ichiro Laruan
Manager, Science & Regulatory Affairs
Biotechnology Innovation Organization



LINE-BY-LINE RECOMMENDED EDITS

SECTION/ LINE	ISSUE	PROPOSED CHANGE
I.	Section 4	
<p>Lines 166-170</p>	<p>“The relevant data and information from the reference product labeling that should be incorporated into the biosimilar and interchangeable biosimilar product labeling will depend on whether the applicant is seeking licensure for all conditions of use (e.g., indication(s), dosing regimen(s)) or fewer than all conditions of use for which the reference product has been previously licensed.”</p> <p>This sentence may suggest that the relevant data and information to include in the biosimilar label is based on a binary question: whether (or not) the biosimilar applicant is seeking licensure for all conditions of use. We recommend reframing the sentence so that it makes clear that the data and information included in the biosimilar label depends on the particular conditions of use for which the applicant is seeking licensure. We also suggest noting strength as another example of a condition of use.</p>	<p>BIO recommends the following changes:</p> <p>“The relevant data and information from the reference product labeling that should be incorporated into the biosimilar and interchangeable biosimilar product labeling will depend on <u>the specific conditions of use for which</u> whether the applicant is seeking licensure for all conditions of use (e.g., indication(s), dosing regimen(s), <u>strength(s)</u>) or fewer than all conditions of use for which the reference product has been previously licensed.”</p>
<p>Lines 411-418</p>	<p>The draft guidance states that the Highlights section of the label of a biosimilar should include the following footnote:</p>	<p>BIO recommends the following changes:</p> <p>“*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved</p>



	<p>“*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of [BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT’S PROPRIETARY NAME] has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in <i>its Full Prescribing Information</i>” (emphasis added).</p> <p>The reference to “its Full Prescribing Information” may be confusing given that this statement appears in the referenced prescribing information itself.</p>	<p>biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of [BIOSIMILAR OR INTERCHANGEABLE BIOSIMILAR PRODUCT’S PROPRIETARY NAME] has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full <u>this</u> Prescribing Information.”</p>
<p>Line 480</p>	<p>Table 4: The scenario for the reference product where the evidence supports the safety and effectiveness for an indication in pediatric patients, the recommended text for the biosimilar or interchangeable biosimilar product labeling is "The safety and effectiveness of NEXSYMEO (for Indication Y) have been established in pediatric patients aged 6 months and older. Use of NEXSYMEO for this indication is supported by NEXSYMEO’s approval as a biosimilar to</p>	<p>BIO recommends the following changes:</p> <p>"The safety and effectiveness of NEXSYMEO (for Indication Y) have been established in pediatric patients aged 6 months and older. Use of NEXSYMEO for this indication is supported by NEXSYMEO’s approval as a biosimilar to replicamab-hjxf and evidence from adequate and well-controlled studies of replicamab-hjxf in adults with additional pharmacokinetic and safety data of replicamab-hjxf in pediatric patients aged 6 months and older.</p>



	<p>replicamab-hjxf and evidence from adequate and well-controlled studies of replicamab-hjxf in adults with additional pharmacokinetic and safety data of replicamab-hjxf in pediatric patients aged 6 months and older."</p> <p>However, there may be situations where some pediatric indication(s) for the reference product is still protected by regulatory exclusivity so the biosimilar or interchangeable biosimilar product labeling cannot have such indication(s) on their label until the expiration of the exclusivity.</p>	<p><u>Pediatric assessments for NEXSYMEO demonstrate that NEXSYMEO is safe and effective for pediatric patients in other indications for which replicamab-hjxf is approved. However, NEXSYMEO is not approved for such indications due to regulatory exclusivity for replicamab-hjxf."</u></p>
--	---	--